PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
	)	Group Art Unit: 1648
Pablo D. GARCIA, *et al.*	)	
	)	Examiner: Humphrey, L.
Serial No. 10/016,604	)	
	)	Atty. Docket No. PP016466.0002
Filed: December 7, 2001	)	
		CONFIRMATION NO. 6543

For: ENDOGENOUS RETROVIRUSES UP-REGULATED IN PROSTATE CANCER

DECLARATION OF PABLO D. GARCIA UNDER 37 C.F.R. § 1.132

U.S. Patent and Trademark Office
401 Dulany Street
Alexandria, VA 22314

Sir:

I, Pablo D. Garcia, am a co-inventor of the above-captioned patent application ("this application"). I am currently employed as Senior Research Investigator II at Novartis Institutes for BioMedical Research, Oncology in Emeryville, California. Novartis is the owner of the present application by virtue of a merger involving Chiron Corporation, the original assignee of this application.

I have extensive knowledge in the fields of molecular biology and genomic oncology, which have been the subjects of my research over the past 20 years. In connection with this work, particularly with respect to gene expression in cancers, I have co-authored numerous publications and am a named inventor on numerous patents and patent applications. My curriculum vitae is attached as Exhibit A.

In this regard, I hereby state and declare as follows:

1. I have reviewed the specification and currently pending claims of this application, in addition to the present claim rejections in the Office Action dated August 20, 2009 ("the Office Action").

2. I understand that the currently pending claims are directed to methods of screening for early stage prostate cancer by assaying an RNA expression product of a particular HML-2 retrovirus, namely HERV-K (CH), in a prostate or blood sample. I also understand that a basis asserted for rejecting these claims is that the specification does not reasonably enable assaying, in a patient blood sample, the RNA of HERV-K (CH) that is at least 150% relative to a control sample level. According to the sentence bridging pages 4 and 5 of the Office Action, "it is unpredictable whether an at least 150% relative higher expression of HERV-K RNA in blood is definitively indicative of prostate tumor but not other types of carcinogenic diseases, such as breast cancer, gastric cancer or trophoblastic disease".

3. As noted above, the currently pending claims recite assaying an RNA expression product of HERV-K(CH) in particular, and not any HERV-K. Therefore, my statements herein address the issue, raised in the Office Action, to the extent of whether higher expression of HERV-K(CH) in blood is specifically indicative of prostate cancer but not other types of cancers.

4. Under my supervision, expression of HERV-K(CH) mRNA was studied using the microarray techniques as described in this application in prostate tumor tissue as well as in tumor samples taken from patients with breast or colon cancer. The results are shown in Table 10 on page 92 and described on page 79, lines 15-21 of the specification of this application. As stated, Table 10 illustrates "Expression of HERV-K viruses in colon and breast tumors." Also, in Table 10, "the "Result" columns give the % of patient samples which showed up-regulation of the GenBank sequence given in the first column in tumor tissue relative to non-tumor tissue." The first row of Table 10 therefore clearly shows that 65% of the prostate tissue samples from patients showed up-regulation of sequences in GenBank ID/Accession AB047240, while 0% of breast tissue samples and 2% of colon tissue samples showed up-regulation of these sequences.

5. The GenBank ID/Accession AB047240 as used in Table 10 of the specification represents HERV-K(CH) sequences. The expression results for sequences in GenBank ID/Accession AB047240, shown in the first row of Table 10, were obtained from the 16 mRNA clones of HERV-K(CH) that (i) are referenced in Tables 4, 5, 6, and 7, as well as Figure 1 of this application and (ii) have sequences described in Table 8 of this application.

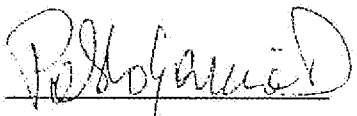
6. Evidence of the association between the GenBank ID/Accession AB047240 and the 16 mRNA clones of HERV-K(CH) is found on page 37 lines 20-21, page 76 line 28 to page 77 line 14, page 78 lines 9-17 and Table 5 on page 87 of the specification. Page 37, lines 20-21 states that sequences from HERV-K(CH) are shown in SEQ IDs 14-39. Page 77, lines 4-5 and 13-14 indicate that SEQ IDs 27-39 were obtained from a first pass sequencing of the PCR products of 16 clones of prostate cancer mRNA expression products disclosed in Table 6 and that SEQ IDs 14-26 were obtained from a second pass sequencing of the same 16 clones. Page 77, lines 9-12 discloses that the 16 clones of HERV-K(CH) have some degree of sequence identity to HERV-K(II) as disclosed in GenBank Accession AB047240. Page 78, lines 9-17 and Table 5 discloses the sequence homologies between the HERV-K(CH) sequences and HERV-K(II) (GenBank Accession AB047240).

7. Additionally, the attached Exhibits B and C, which were generated under the supervision of myself and the other named inventors of this application prior to September 8, 2000, further evidences the association between GenBank ID/Accession AB047240 and the 16 mRNA clones of HERV-K(CH). Exhibit B shows the upregulated mRNA expression products detected in 12 of 13 prostate cancer patients studied. Exhibit B demonstrates that sequences of the first 16 clones, the same 16 clones referred to in Paragraph 5 above, retrieved GenBank ID/Accession AB047240 as the most homologous accession from a sequence homology search in GenBank performed at the time when the subject work was carried out. Exhibit C clearly illustrates the identity/alignment between these 16 clones of HERV-K(CH) and GenBank ID/Accession AB047240.

8. Based on the experimental results described in Paragraph 4 above and shown in Table 10 of the specification, HERV-K(CH) expression products are up-regulated in tissue from prostate tumors, but not in tissue from colon or breast tumors.

9. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: Jan 13, 2010

Signature: 

Pablo D. Garcia, Ph.D.

Exhibit A

Curriculum Vitae
Pablo D. Garcia, Ph.D.
(December, 2009)

Date of Birth: January 19, 1957.

Place of Birth: Viña del Mar, Chile.

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Education:

1979 B.S. in Biology, Catholic University of Valparaiso, Chile.

1982 M.S. in Genetics, Catholic University of Valparaiso, Chile.

1988 Ph.D. in Biochemistry, University of California, San Francisco

Positions and Work Experience:

2006-Present.
Sr. Research Investigator II. Novartis Institutes of Biomedical Research, Oncology.

2005-2006.
Director of Research. Chiron Biopharma Research and Development. Chiron Corporation.

2001-2005.
Associate Director of Research. Chiron Biopharma Research and Develpment . Chiron Corporation.

1999-2001.
Senior Scientist. Chiron Research and Develpment. Chiron Corporation.

1997-1999.
Principal Scientist. Chiron Research and Development. Chiron Corporation.

1994 - 1997.
Post-Graduate Researcher in the laboratory of Dr. Henry R. Bourne, Department of Cellular and Molecular Pharmacology, University of California, San Francisco.

1989 - 1993.
Post-Doctoral fellow in the laboratory of Dr. Richard M. Myers. Department of Physiology, University of California, San Francisco.

1983 - 1989.
Graduate Student, Department of Biochemistry, University of California, San Francisco. Thesis work conducted in the laboratory of Dr. Peter Walter.

1982 - 1983.
Researcher in the laboratory of Dr. William J. Rutter at the Department of Biochemistry, University of California, San Francisco.

1979 - 1981.
Research and Teaching Instructor. Department of Biology, Catholic University of Valparaiso, Chile.

1977 - 1979.
Teaching Assistant for the course of genetics. Department of Biology, Catholic University of Valparaiso, Chile.

Published Patent Applications:

EP 0 948 531	Secreted Human Proteins.
EP 1 053 319	Human Genes and Gene Expression Products II.
EP 1 062 339	Human FGF Gene and Gene Expression Products.
EP 1 105 474	Human Genes and Gene Expression Products V.
EP 1 144 636	Human Genes and Gene Expression Products.
EP 1 177 287	Secreted Human Proteins.
EP 1 190 058	Human Genes and Gene Expression Products I.
EP 1 194 549	Human Genes and Gene Expression Products.
WO 98/25959	Secreted Human Proteins.
WO 99/33982	Human Genes and Gene Expression Products.
WO 99/38972	Human Genes and Gene Expression Products II.
WO 99/46381	Human FGF Gene and Gene Expression Products.
WO 99/58675	Human Genes and Gene Expression Products V.
WO 00/18916	Human Genes and Gene Expression Products.
WO 00/61755	Secreted Human Proteins.
WO 01/02568	Novel Human Genes and Gene Expression Products.
WO 01/25489	Diagnostic and Therapeutic uses for a Gene Differentially Expressed in Prostate Cancer.
WO 01/66753	Human Genes and Gene Expression Products.
WO 01/72781	Human Genes and Gene Expression Products XVI.

WO 02/06340	Tetraspan Protein and Uses Thereof.
WO 02/14500	Human Genes and Gene Expression Products
JP 2001-505783 T2	Secreted Human Proteins
JP 2002-500010 T2	Human Genes and Gene Expression Products I.
10/016604	Endogenous Retroviruses Up-Regulated in Prostate Cancer
09/872850	Gene Products Differentially Expressed in Cancerous Colon Cancer Cells, and Their Methods of Use
10/616900	Gene Products Differentially Expressed in Cancerous Colon Cancer Cells, and Their Methods of Use
10/310673	Gene Products Differentially Expressed in Cancerous Prostate Cells and Their Methods of Use [C4S2]
09/932076	Human Genes and Gene Expression Products
10/615618	Human Genes and Gene Expression Products
10/609021	Human Genes and Gene Expression Products XVI
10/629771	Novel Human Genes and Gene Expression Products
09/297648	Novel Human Genes and Gene Expression Products II
09/313292	Novel Human Genes and Gene Expression Products V
10/830942	TetraSpan Protein and Uses Thereof
US2005186212A	Trefoil Factor 3 [TFF3] as a Target for Anti-Cancer Therapy
PCT/US2004/043726	Nucleic Acid Based Assays for Identification of FC Receptor Polymorphisms
US2006275747A	Endogenous retrovirus up-regulated in prostate cancer

Publications:

1. **Garcia, P.**, Horvat, A. & Marshall, S. (1982). Potencialidad mutagenica de pesticidas usados en Chile. *An. Mus. Hist. Nat. (Valparaiso, Chile)* **15**, 31-36.

2. Shaul, Y., Ziemer, M. **Garcia, P.D.**, Crawford, R., Hsu, H., Valenzuela, P. & Rutter, W. J. (1984). Cloning and analysis of integrated hepatitis virus sequences from a human hepatoma cell line. *J. Virol.* **51**, 776-787.

3. Ziemer, M., **Garcia, P.D.**, Shaul, Y. & Rutter, W. J. (1985). Sequence of the hepatitis B virus DNA incorporated into the genome of a human hepatoma cell line. *J. Virol.* **53**, 885-892.

4. Lauffer, L., **Garcia, P.D.**, Harkins, R. N., Coussens, L., Ullrich, A. & Walter, P. (1985). Topology of the SRP receptor in the endoplasmic reticulum membrane. *Nature* **318**, 334-338.

5. Hansen, W., **Garcia, P.D.**, & Walter, P. (1986). In vitro protein translocation across the yeast endoplasmic reticulum: ATP-dependent post-translational translocation of the prepro-α-factor pheromone. *Cell* **45**, 397-406.

6. Shaul, Y., **Garcia, P.D.**, Schonberg, S., and Rutter, W.J. (1986). Integration of Hepatitis B Virus DNA in chromosome-specific satellite sequences. *J. Virol.* **59**, 731-734.

7. **Garcia, P.D.**, Ghrayeb, J., Inouye, M. & Walter, P. (1987). Wild type and mutant signal peptides of E.coli outer membrane lipoprotein efficiently interact with mammalian signal recognition particle. *J. Biol. Chem.* **262**, 9463-9468.

8. **Garcia, P.D.**, Ou, J.H., Rutter, W.J., and Walter, P. (1988). Targeting of the hepatitis B virus precore protein to the endoplasmic reticulum membrane: After signal peptide cleavage translocation can be aborted and the product released into the cytoplasm. *J. Cell Biol.* **106**, 1093-1104.

9. **Garcia, P.D.** and Walter, P. (1988). Full-length prepro-α-factor can be translocated across the mammalian microsomal membrane only if translation has not terminated. *J. Cell Biol.* **106**, 1043-1048.

10. Edwards, R.H., Selby, M.J., **Garcia, P.D.** and Rutter, W.J. (1988). Processing of the native NGF precursor to form biologically active NGF. *J. Biol. Chem.* **263**, 6810-6815.

11. Kassenbrock, C.K; **Garcia, P.D.**; Walter, P. and Kelly, R. (1988). Heavy-chain binding protein recognizes aberrant polypeptides translocated in vitro. *Nature* **333**, 90-93.

12. **Garcia, P.D.**, Hansen, W. and Walter, P. (1991). *In vitro* protein translocation across microsomal membranes of *Saccharomyces cerevisiae*. *Methods in Enzymology* **194**, 675-682.

13. Rajpara, S.M., **Garcia, P.D.**, Roberts, R., Eliassen, J.C., Owens, D.F., Maltby, D., Myers, R.M. and Mayeri, E. (1992). Identification and molecular cloning of a neuropeptide Y homolog that produces prolonged inhibition in *Aplysia* neurons. *Neuron* **9**, 505-513.

14. **Garcia, P.D.** and Myers, R.M. (1994). Pituitary Cell line GH3 Expresses two Somatostatin Receptor Subtypes that Inhibit Adenylyl Cyclase: Functional Expression in HEK-293 Cells of Rat Somatostatin Receptor Subtypes SSTR1 and SSTR2. *Mol. Pharmacol.* **45**, 402-409.

15. Forsayeth, J.R. and **Garcia, P.D.** (1994). Adenovirus-Mediated transfection of cultured cells. *Biotechniques*. **17**, 354-359.

16. **Garcia, P.D.**, Onrust, R., Bell, S.M., Sakmar, T.P. and Bourne, H.R. (1995). Transducin-α C-Terminal Mutations Prevent Activation by Rhodopsin. A New Assay Using Recombinant Proteins Expressed in Cultured Cells. *EMBO J.* **14**, 4460-4469.

17. Onrust, R., Herzmark, P., Chi, P., **Garcia, P.D.**, Lichtarge, O., Kingsley, C. and Bourne, H.R. (1997). Receptor and βγ Binding Sites in the α Subunit of the Retnal G Protein Transducin. *Science*, 275, 381-384.

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19. Easwaran, V., Lee, S.H., Inge, L., Guo, L., Goldbeck, C., Garrett, E., Wiesmann, M., **Garcia, P.D.**, Fuller, J.H., Chan, V., Randazzo, F., Gundel, R., Warren, R.S., Escobedo, J., Aukerman, S., Taylor, R.N. and Fantl, W.J. (2003). β-Catenin Regulates Vascular Endothelial Growth Factor (VEGF-A) Expression in Colon Cancer. *Cancer Research*, **63**: 3145-3153.

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Articles in Books:

1. Shaul, Y., Standring, D., Ziemer, M., **Garcia, P.D.**, Hsu, H., Laub, O., Rall, L., Valenzuela, P., & Rutter, W. J. (1983). Transcription and integration of hepatitis B virus. In Viral Hepatitis: Second International Max von Pettenkofer Symposium. (eds: L. R. Overby, F. Deinhardt & J. Deinhardt), Marcel Dekker, Inc., New York, pp. 71-77.

2. Rutter, W. J., Ziemer, M., Ou, J., Shaul, J., Laub, O., **Garcia, P.D.** & Standring, D. N. (1984). Transcription units of hepatitis B Virus genes and structure and expression of integrated viral sequences. In Liver Hepatitis and Liver Disease. Grune & Stratton.

3. Walter, P., Siegel, V., Lauffer, L., **Garcia, P.D.**, Ullrich, A. & Harkins, R. (1985). Targeting of nacent secretory proteins to the endoplasmic reticulum membrane. In Transport and secretion of proteins (Ed: M. J. Gething), Cold Spring Harbor Press, New York, pp. 21-23.

4. Walter, P., Siegel, V., Lauffer, L. & **Garcia, P.D.** (1986). The protein translocation machinery of the endoplasmic reticulum -- The signal hypothesis ten years later. In protein compartmentalization (Eds: I. Boime, A. Strauss & G. Kreil), Springer-Verlag, New York, pp. 1-13.

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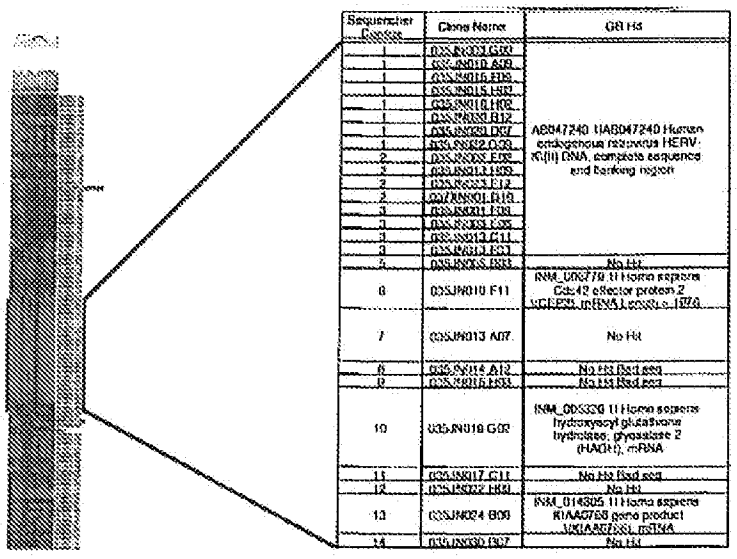
EXHIBIT B*

Upregulated mRNA Expression Products Detected in Prostate Cancer Patients



Sequencher Family	Clone Name	GB Hit
1	035JN003 G09	AB047240 /IAB047240 Human endogenous retrovirus HERV-K(III) DNA, complete sequence and flanking region
1	035JN010 A09	
1	035JN015 B05	
1	035JN015 H03	
1	035JN018 H05	
1	035JN028 B12	
1	035JN029 D07	
1	035JN032 C09	
2	035JN005 E05	
2	035JN011 H09	
2	035JN023 E12	
2	037JN001 B10	
3	035JN001 H09	
3	035JN003 F05	
3	035JN013 C11	
3	035JN013 F03	
5	035JN005 B03	No Hit
6	035JN010 F11	NM_006779.1 Homo sapiens Cdc42 effector protein 2 (CEP2), mRNA / gi|5174
7	035JN013 A07	No Hit
8	035JN014 A12	No Hit Bad seq
9	035JN018 H03	No Hit Bad seq
10	035JN018 G03	NM_005329.1 Homo sapiens hydroxyacyl glutathione hydrolase, glyoxalase 2 (HAGH), mRNA
11	035JN017 C11	No Hit Bad seq
12	035JN022 H03	No Hit
13	035JN024 B09	NM_014805.1 Homo sapiens KIAA0768 gene product (KIAA0768), mRNA
14	035JN030 D07	No Hit

***The red color intensity reflects the level of upregulation in cancer tissues relative to normal prostate cells.**

EXHIBIT C

Alignment between HERV-K(CH) Expression Products and GenBank ID/Accession AB047240